REMARKS

Claims 1-3, 6, 8, 14-17 and 19-37 are pending and under examination in the subject application. Claims 29 and 30 are allowed. Applicants have hereinabove amended claims 1, 14, 17, 28, and 30-32. Applicants have amended claims 17, 30, and 32 to make certain formatting changes. Accordingly, upon entry of this Amendment, claims 1-3, 6, 8, 14-17, 19-28 and 31-37 will be pending and under examination.

In making these amendments, applicants neither concede the correctness of the Examiner's rejections in the December 2, 2003 Office Action, nor abandon the right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. Applicants maintain that these amendments to the claims do not raise any issue of new matter, and that these claims are fully supported by the specification as originally filed. Accordingly, applicants respectfully request that this Amendment be entered.

In view of the remarks set forth below, applicants maintain that the Examiner's outstanding objection and rejections have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

The Claimed Invention

This invention provides a small molecular weight tumor necrosis factor (TNF) receptor molecule and related methods. This receptor molecule binds TNF and comprises

all or a functional portion of at least two extracellular domains of TNF receptors linked via one or more polypeptide linkers. The polypeptide linkers are from about 10 to about 30 amino acids in length.

The claimed receptor molecule shows *surprising* advantages over other multi-TNF receptor-based molecules. Specifically, the instant molecule, as exemplified by Hu TNF-R75 ECD, shows the same anti-TNF-specific activity as an Ig-based TNF receptor molecule - and at *only a third of the concentration* required for the Ig-based molecule. Even more dramatic is the fact that a concentration of TNF receptor monomer 300-fold higher than that tested for the instant molecule *was ineffective*.

The claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

Formalities

The Examiner objected to claim 14 since it recites "Isolated DNA comprising a receptor molecule." The Examiner asserts that DNA does not comprise a protein, and therefore, requires appropriate correction to claim 14.

In response, applicants note that amended claim 14 does not recite "Isolated DNA comprising a receptor molecule."

Thus, the Examiner's objection of claim 14 is obviated.

Rejection Under 35 U.S.C. §112, Second Paragraph - Indefiniteness

The Examiner rejected claims 14, 28 and 31-37 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner asserts that claims 14 and 28 are indefinite because they encompass a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation in the same claim. The Examiner also asserts that claim 31 is indefinite because it encompasses a method of making a construct to express the protein of SEQ ID NO: 2, which consists of two extracellular domains of TNF, but the method of dependent claim 31 is drawn to making a construct comprising three extracellular domains of TNF.

In response to the Examiner's rejection to claims 14, 28 and 32-37, applicants respectfully traverse, noting that neither amended claims 14 or 28 recite a broad range or limitation, i.e., a DNA molecule encoding a protein comprising a polypeptide linker wherein the linker is from about 10 to about 30 amino acid residues in length, together with a narrow range or limitation, i.e., that the DNA comprises SEQ ID NO: 1 or the protein has the sequence of SEQ ID NO: 2, respectively, that falls within the broad range or limitation in the same claim. Thus, the Examiner's rejection of claims 14, 28 and 32-37 is obviated.

In response to the Examiner's rejection to claim 31, applicants again respectfully traverse, noting that amended claim 31 is no longer dependent to claim 30, and therefore, the Examiner's rejection of claim 31 is obviated.

In view of the above remarks, applicants maintain that claims 14, 28 and 31-37 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §103 - Obviousness

The Examiner rejected claims 1-3, 6, 8, 15-17 and 19-27 under 35 U.S.C. §103 as allegedly obvious over Wallace et al. (U.S. Patent No. 5,478,925; "Wallace I"), or Wallace et al. (European Patent No. 0 526 905; "Wallace II"), in view of Paul et al. (U.S. Patent No. 5,736,387; "Paul").

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness. Applicants incorporate herein by reference their remarks in the September 2, 2003 Communication, the August 19, 2002 Communication, and the October 15, 2001 Amendment made in connection with the non-obviousness of the claimed subject matter, and make the following additional remarks to underscore their position.

Again, claims 1-3, 6, 8, 15-17 and 19-37 provide a small molecular weight TNF receptor-based molecule and methods of using same. This molecule binds TNF and comprises all or a functional portion of at least two extracellular

domains of TNF receptors linked via one or more polypeptide linkers of about 10 to about 30 amino acids in length.

As stated earlier, the claimed molecule is characterized by a low molecular weight, an optimal linker length, and the absence of an Ig Fc domain which has the potential to cause side effects. These features combined make this molecule unexpectedly superior to known TNF receptor-based molecules.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every limitation of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, one of ordinary skill would have to have been motivated to combine the teachings of the cited references at the time of the invention. Moreover, these references would also have to provide a reasonable expectation of success.

Applicants point out that the Examiner's combination of cited references is based on an improper use of hindsight, and that these references are devoid of any

motivation to combine their respective teachings. In essence, the cited references mention polypeptide linkers *in general*, and lack a specific teaching, suggestion or incentive to create a TNF-based molecule comprising all or a functional portion of at least two extracellular domains of TNF receptors linked via one or more polypeptide linkers of about 10 to about 30 amino acids in length. This notion is further elaborated upon below.

Wallace I and II teach TNF receptor multimers that are made from monomers held together *by any means* (see Wallace I, column 4, lines 14-17; Wallace II, page 2, lines 44-46). For example, the monomers may be held together by both covalent bonding, such as via chemical cross-linkers, as well as non-covalent bonding, such as via liposome formation. (See Wallace I, column 9, line 4 to column 10, line 34; Wallace II, page 6, line 29 to page 7, line 48). As stated in previous responses, joining monomers covalently via a peptide linker is but only one method out of a veritable universe of possibilities taught by the Wallace I and II. Furthermore, nowhere in either Wallace I or II does it suggest a linker length or an amino acid makeup for optimum activity. These references offer no experimental evidence demonstrating the success of their claimed multimers. They also fail to give guidance as to how one would arrive at a linker length or an amino acid makeup which would provide the unexpected advantage seen with the instant invention. At most, the possibility that one skilled in the art could have optimized a linker length and an amino acid makeup using routine experimentation is merely an invitation to experiment further.

Paul teaches retroviral vectors having on its surface chimeric targeting proteins that bind to specific target cells via cellular cytokine receptors and mediating vector entry into the targeted cells. Paul presents a large number of permutations of linkers or "flexons" in chimeric targeting proteins for retroviral vectors without providing guidance as to how one would arrive at a linker length or an amino acid makeup which would provide the unexpected advantage seen with the instant invention. Specifically, Paul teaches that a flexon can be made up of a majority of amino acids with small side chains *such as* glycine, alanine, valine, leucine, isoleucine and serine, and that the flexon should range from "4 to 100 amino acids" in length. (Paul, column 11, lines 5-42 and column 20, lines 34-54). Moreover, nowhere does Paul suggest or mention TNF receptor-based molecules.

The instant invention provides one of a veritable universe of combinations of individual components disclosed in Wallace I, Wallace II and Paul. Some motivation to select a *particular* combination in view of a given large group of possibilities must be taught by the prior art.

Furthermore, according to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the

combination."

In re Mills, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of the applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of many possible choices is likely to be successful" to one skilled in the art to create a small molecular weight TNF comprising all or a functional portion of two or more extracellular domains of TNF receptor linked to a polypeptide linker of about 10 to about 30 amino acids in length. (*In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).) Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result. Devoid of any support to the contrary, an "invitation to try," which applicants do not concede exists, is considered inadequate support for an obviousness rejection. (*Id.*)

Finally, applicants note that the claimed invention demonstrates an unexpected advantage, e.g., the increased efficiency in anti-TNF specific activity relative to recombinant Ig-based molecules as evidenced on page 18, lines 3-24 and Table 1 of the instant application. In Table 1, the claimed invention shows the same anti-TNF

specific activity but at *only a third of the concentration* required for the Ig-based molecule. Page 18, lines 3-24 and Table 1 also show that the instant invention, as demonstrated by Hu p75 TNF-R ECD, is *surprisingly* capable of binding to the TNF homotrimer in a stoichiometric ratio of almost 1:1. This surprising result is even more dramatic when noting that a concentration of TNF receptor monomers 300-fold higher than that tested for the instant invention *was ineffective*. To the extent a proper *prima facie* case were made by the Examiner, which, again, applicants do not concede, this evidence of an unexpected advantage, i.e., increased efficiency in anti-TNF specific activity relative to recombinant Ig-based molecules, would overcome such case. (See M.P.E.P. §716.02.)

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art would *not* have been able to predict, based on the cited references, whether a linker length of about 10 to about 30 amino acids is an optimal length for a TNF receptor-based molecule is *more effective* than linkers of different lengths. Moreover, one of ordinary skill certainly would not have reasonably expected the superior effects of linker length in the claimed invention as discussed above. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 15-17 and 19-27 over the cited references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

The Examiner also rejected claims 1-3, 6, 8, 15-17 and 19-27 under 35 U.S.C. §103 as allegedly obvious over Smith et al. (U.S. Patent No. 5,395,760; "Smith") in view of Paul.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

The rejected claims are discussed above.

Smith suffers the same deficiency found in Wallace I and II, i.e., it teaches a receptor-based molecule with a virtually infinite number of linker permutations. Smith teaches that "both monovalent and polyvalent forms of TNF-R are useful in the composition and methods of the invention...[f]or example, a bivalent soluble TNF-R may consist of two tandem repeats of amino acids 1-235 of FIG. 2A, separate by a linker region." (See Smith, column 10, lines 33-39). However, Smith does not define the optimal length of this linker region. Instead, Smith focuses on providing examples of polyvalent forms of TNF-R constructed by chemical coupling techniques. Smith also fails to give guidance as to how one would arrive at a linker length or an amino acid makeup which would provide the unexpected advantage seen with the instant invention.

Paul is discussed above.

Smith and Paul ultimately fail to provide a motivation or

suggestion to combine the teachings of the cited references for the same reasons cited above. To maintain otherwise would be impermissible hindsight.

Finally, applicants again note that the claimed invention demonstrates unexpected advantages, as discussed above in detail. To the extent a proper *prima facie* case were made by the Examiner, which, again, applicants do not concede, the unexpected advantages of this invention would overcome such case. (See M.P.E.P. §716.02.)

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 1-3, 6, 8, 15-17 and 19-27 over the cited references. For the same reasons, applicants alternatively maintain that the rejected claims would not have been obvious over these references.

In view of the above remarks, applicants maintain that claims 1-3, 6, 8, 15-17 and 19-27 satisfy the requirements of 35 U.S.C. §103.

Summary

Applicants maintain that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

3/2/04

Alan J. Morrison — Date
Reg. No. 37,399